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Gut Microbiota as a Determinant of Therapeutic Response in Chronic Diseases: From Systemic Dysbiosis to Microbiome-Guided Precision Medicine

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Abstract: Growing evidence indicates that gut microbiota dysbiosis plays a central role in the development and progression of chronic systemic diseases through metabolic, immunological, and inflammatory pathways. Beyond its contribution to disease pathophysiology, recent clinical studies suggest that gut microbiota composition may also determine individual responses to dietary and pharmacological interventions. This integrative review synthesizes current evidence linking microbial imbalance to metabolic disorders, diabetes mellitus, obesity, musculoskeletal diseases, and functional systemic syndromes, while highlighting emerging findings from randomized clinical trials demonstrating microbiota-dependent variability in glycemic response to dietary fiber and modern glucose-lowering agents such as GLP-1 receptor agonists and SGLT2 inhibitors. Baseline microbial profiles have been shown to predict treatment efficacy and therapeutic outcomes, supporting the concept of microbiota-informed stratification in clinical decision-making. These findings suggest that interindividual differences in microbiome composition may underlie heterogeneous responses to standardized interventions and pharmacotherapies. Advances in multi-omics technologies, machine learning models, and microbiota-derived biomarkers may enable personalized therapeutic strategies capable of modifying disease trajectories rather than merely managing symptoms. Integrating microbiota profiling into preventive and therapeutic frameworks may therefore represent a critical step toward microbiome-guided precision medicine in chronic systemic diseases.

Keywords: Dysbiosis, Metabolic Disorders, Microbiome Biomarkers, Microbiome-Guided Therapy, Personalized Nutrition, Pharmacomicribiomics.

Research Paper

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1.0. INTRODUCTION

The human gut microbiota has emerged as a central biological system involved in the regulation of the immune system, the maintenance of metabolic homeostasis, and the control of inflammatory processes. Rather than acting as a passive microbial community, intestinal microorganisms interact dynamically with host tissues through complex metabolic and immunological mechanisms. Disruption of this finely balanced equilibrium, known as dysbiosis, has been increasingly associated with the development and progression of chronic systemic diseases affecting multiple organ systems. The gut microbiota, therefore, functions as a central regulator of systemic homeostasis (Hay, 2017; Manning and Kowalska, 2021; Nekoukar *et al.*, 2021; Biderman, 2023).

Importantly, emerging evidence suggests that the clinical relevance of gut microbiota extends beyond its contribution to disease pathophysiology, encompassing a modulatory role in individual responses to dietary and pharmacological interventions. Variations in microbial composition and metabolic activity have been associated with heterogeneous therapeutic outcomes across patients receiving standardized nutritional strategies or pharmacological treatments for metabolic disorders, particularly type 2 diabetes mellitus. In this context, the gut microbiome has been increasingly investigated as a potential predictive biomarker capable of influencing treatment efficacy, drug metabolism, and metabolic responsiveness (Figure 1) (Gurung *et al.,* 2020; Fan and Pedersen, 2021; Valdes *et al.,* 2021; Lynch and Pedersen, 2024).

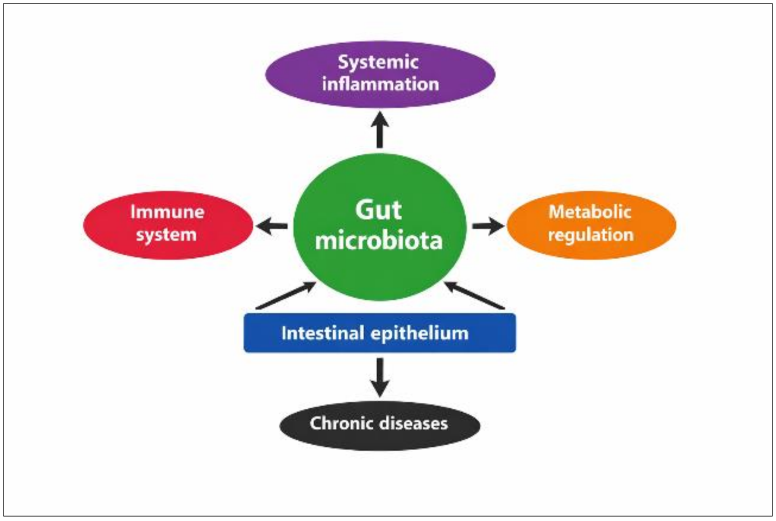

Figure 1: Schematic representation of the gut microbiota as a central axis integrating intestinal barrier function, immune modulation, and metabolic regulation. Microbiota-driven interactions contribute to systemic inflammatory signaling. These processes influence the development and progression of chronic diseases

Recent advances in microbiome profiling, multi-omics technologies, and machine learning approaches have enabled the identification of microbial signatures associated with differential responses to dietary fiber intake and glucose-lowering agents, including GLP-1 receptor agonists and sodium–glucose cotransporter-2 inhibitors (Song *et al.,* 2025; Klemets *et al.,* 2026; Wen, 2026). These findings support the emerging concept that baseline microbiota composition may inform individualized therapeutic strategies, shifting current paradigms from uniform intervention models toward microbiome-guided precision medicine frameworks (Valdes *et al.,* 2021; Lynch and Pedersen, 2024).

Accumulating evidence suggests that gut microbiota dysbiosis contributes to the development of chronic inflammation by increasing intestinal permeability and facilitating the translocation of microbial products into the systemic circulation. This persistent low-grade inflammatory state has been implicated as a shared mechanistic pathway linking metabolic, autoimmune, and degenerative disorders. Such alterations in host–microbe interactions reinforce the concept of the gut as a critical interface between environmental exposures and the systemic expression of disease. Core biological components of the inflammatory process (Figure 2) (Cani *et al.*, 2019; Zheng *et al.*, 2020; Belkaid and Harrison, 2021; Fan and Pedersen, 2021).

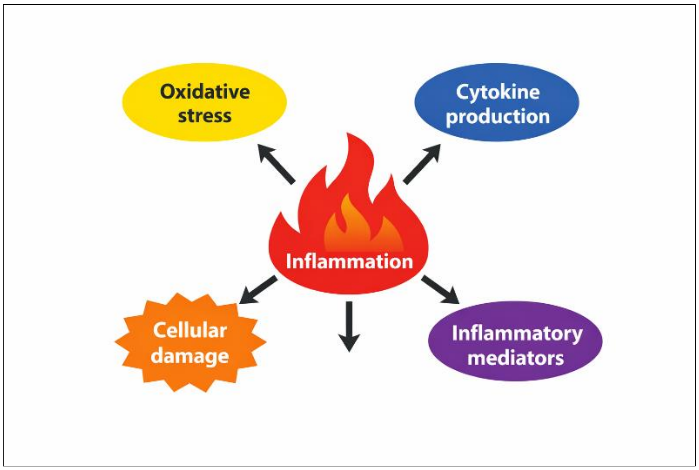

Figure 2: Schematic representation of inflammation highlighting oxidative stress, cytokine production, cellular damage, and inflammatory mediators as interconnected components. These elements interact dynamically to sustain and amplify inflammatory responses. The figure emphasizes inflammation as a central integrative biological process

Beyond inflammatory signaling, the gut microbiota exerts a direct influence on host metabolism through the production of bioactive compounds, including short-chain fatty acids and other microbial metabolites. These substances play a key role in regulating energy balance, glucose homeostasis, and lipid metabolism, thereby linking microbial composition to metabolic disorders such as obesity and diabetes mellitus. This metabolic dimension further reinforces the concept of the microbiota as an active modulator of systemic physiological processes rather than a secondary bystander. Key mechanisms linking the gut microbiota to metabolic dysfunction (Figure 3) (Turnbaugh *et al.*, 2009; Tremaroli and Bäckhed, 2012; Koh *et al.*, 2016; Fan and Pedersen, 2021).

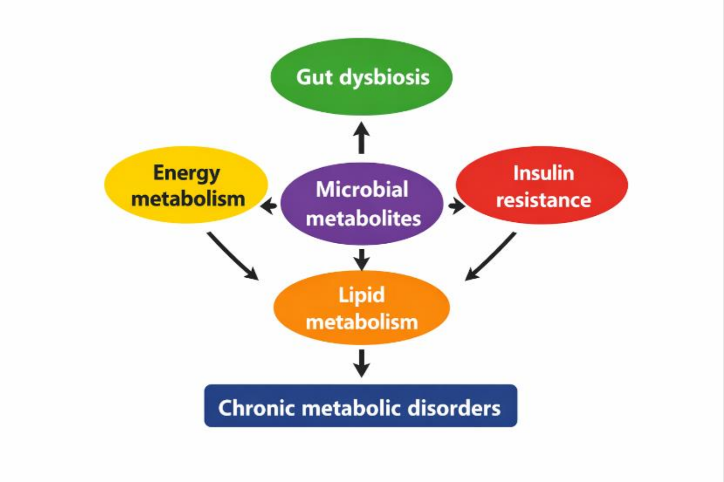

Figure 3: Schematic representation of microbial and host components involved in energy metabolism, glucose regulation, and lipid homeostasis. Interactions between microbial metabolites and host pathways contribute to metabolic imbalance. These mechanisms highlight the role of gut dysbiosis in metabolic disease development

Growing evidence also links gut microbiota alterations to musculoskeletal and autoimmune conditions, including inflammatory arthritis and osteoarthritis, through immune-mediated and metabolic pathways. Microbial-derived signals have been shown to modulate joint inflammation, cartilage degradation, and pain perception, thereby supporting the existence of a gut–joint axis. These observations extend the relevance of intestinal dysbiosis beyond metabolic disease, positioning it as a contributor to systemic inflammatory and degenerative processes. Gut microbiota–immune system interactions at the intestinal interface (Figure 4) (Scher *et al.*, 2013; Boer *et al.*, 2019; Favazzo *et al.*, 2020; Huang *et al.*, 2022; Santana *et al.*, 2024).

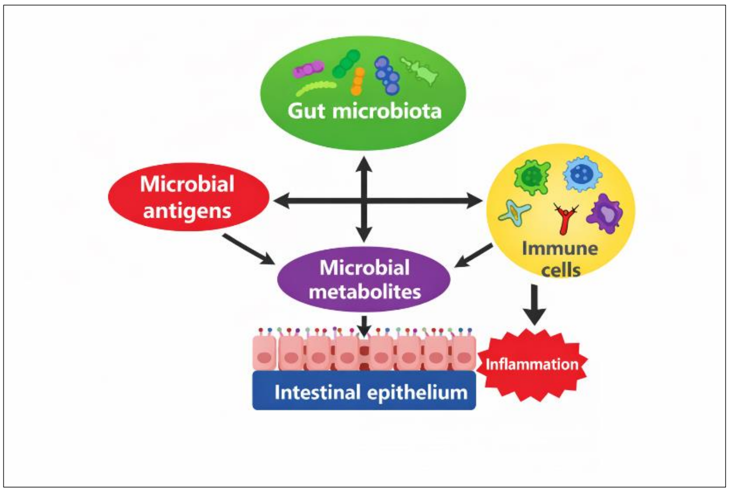

Figure 4: Schematic representation of interactions between gut microbiota, microbial antigens, microbial metabolites, and immune cells at the intestinal epithelium. These interactions modulate immune activation and inflammatory responses. The figure highlights the central role of microbiota-driven signaling in intestinal and systemic inflammation

In addition to metabolic and inflammatory effects, growing evidence suggests that the gut microbiota may exert a functional and, in some contexts, causal role in specific systemic syndromes. Certain microbial taxa are capable of producing bioactive or toxic metabolites that directly affect host physiology, demonstrating that microbial activity can generate disease phenotypes rather than merely modulate disease risk. This concept of functional causality represents a significant shift in microbiota research, underscoring the need to evaluate mechanistic pathways that extend beyond purely associative correlations (Figure 5) (Turnbaugh *et al.*, 2009; Tremaroli and Bäckhed, 2012; Fan and Pedersen, 2021; Zhao *et al.*, 2023).

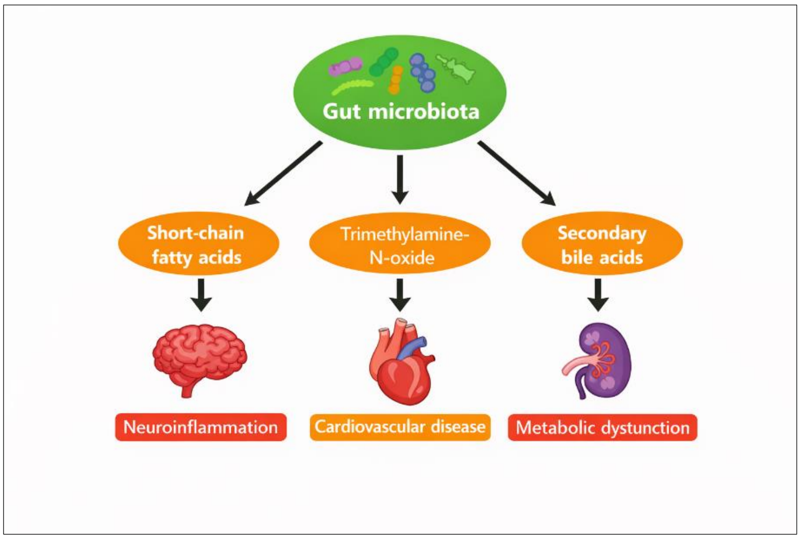

Figure 5: Schematic representation of microbial metabolic activity leading to the endogenous production of bioactive or toxic metabolites. These metabolites interact with host tissues and physiological systems. The figure highlights microbiota-driven functional mechanisms underlying systemic clinical manifestations

Based on this expanding body of evidence, the present study aims to provide an integrative analysis of the gut microbiota as a central driver of systemic inflammation, metabolic dysfunction, musculoskeletal disease, and functional syndromes. By synthesizing findings across metabolic, immunological, and clinical domains, this review seeks to move beyond isolated disease models toward a unified, systems-based perspective. Such an approach is essential to support translational strategies targeting the microbiota for the prevention, diagnosis, and therapeutic intervention of chronic diseases. Gut–brain axis mediated by microbiota signaling pathways (Figure 6) (Qin *et al.*, 2010; Belkaid and Harrison, 2017; Fan and Pedersen, 2021; Lynch and Pedersen, 2024).

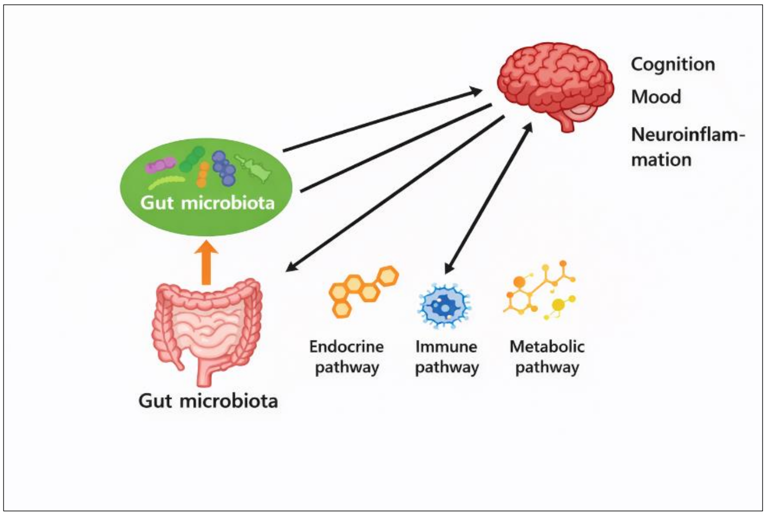

Figure 6: Schematic representation of interactions between gut microbiota and the central nervous system through neural, endocrine, immune, and metabolic pathways. Microbiota-derived signals influence cognitive function, mood regulation, and neuroinflammatory processes. The figure highlights the integrative role of the gut–brain axis in systemic homeostasis

The primary objective of this study is to provide an integrative, system-oriented analysis of the gut microbiota as a central driver of systemic inflammation and chronic disease, in line with its emerging role in immune regulation, metabolic homeostasis, and host–microbe interactions. Specifically, this review aims to examine the contribution of the intestinal microbiota to metabolic disorders, musculoskeletal and autoimmune conditions, functional systemic syndromes, and dysregulated inflammatory pathways. By synthesizing evidence across immunological, metabolic, and clinical domains, this work seeks to support a unified, systems-based framework for understanding microbiota-mediated disease mechanisms and their implications for prevention, diagnosis, and therapeutic strategies.

2.0. METHODS

This study was designed as an integrative narrative review aimed at synthesizing current scientific evidence on the role of the gut microbiota in systemic inflammation and chronic disease. The integrative approach was selected to allow the inclusion of experimental, clinical, and epidemiological studies addressing metabolic, musculoskeletal, autoimmune, and functional systemic conditions. This methodological framework enables a comprehensive evaluation of diverse study designs while supporting critical comparison across biological and clinical domains. A systematic search strategy was conducted across major scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify relevant literature published between 2010 and 2026. Search terms were defined as *a priori* and combined using Boolean operators, with a focus on keywords related to gut microbiota, systemic inflammation, metabolic disorders, musculoskeletal disease, and functional syndromes. Additional articles were identified through manual screening of reference lists to ensure comprehensive coverage of the topic.

Eligibility criteria were established to include original research articles, reviews, and relevant observational or experimental studies addressing the relationship between gut microbiota and systemic disease. Studies focusing exclusively on localized gastrointestinal conditions without systemic implications were excluded, as were reports lacking sufficient methodological clarity. Only publications written in English were considered to ensure consistency in data interpretation and synthesis. Data extraction was performed using a standardized framework to collect information on study design, population characteristics, main outcomes, and proposed biological mechanisms. The selected studies were analyzed through qualitative thematic synthesis, allowing integration of findings across metabolic, immunological, and clinical domains. This approach facilitated the identification of convergent patterns while acknowledging heterogeneity in study designs and inherent methodological limitations.

3.0. RESULTS

Analysis of the selected studies demonstrated that gut microbiota dysbiosis was consistently associated with the presence of systemic low-grade inflammation across multiple chronic conditions. Alterations in microbial composition were frequently linked to increased intestinal permeability and the systemic dissemination of inflammatory mediators. These findings indicate that dysbiosis represents a common biological feature underlying diverse metabolic, autoimmune, and degenerative disease profiles.

Across the analyzed literature, reduced microbial diversity and shifts in key bacterial taxa were recurrently observed in individuals with chronic inflammatory states. Several studies highlighted the role of microbial-derived metabolites, such as short-chain fatty acids and lipopolysaccharides, in modulating immune activation and inflammatory signaling pathways. In parallel, dysregulated host–microbe interactions were shown to influence metabolic homeostasis, insulin sensitivity, and lipid metabolism, further reinforcing the systemic impact of intestinal microbial imbalance. Collectively, these results support the concept that gut microbiota dysbiosis contributes not only to disease-specific mechanisms but also to shared pathophysiological processes underlying chronic systemic disorders (Table 1).

Table 1: Gut microbiota dysbiosis and systemic low-grade inflammation across chronic conditions. This table summarizes shared dysbiotic patterns and systemic inflammatory outcomes

Disease context	**Microbiota alteration**	**Barrier integrity**	**Inflammatory profile**	**Systemic outcome**
Metabolic disorders	Reduced diversity	Increased permeability	Low-grade inflammation	Systemic inflammation
Obesity	Pro-inflammatory taxa	Compromised junctions	Chronic activation	Metabolic imbalance
Diabetes mellitus	Dysbiotic profiles	Altered epithelium	Insulin-linked inflammation	Metabolic dysregulation
Autoimmune diseases	Loss of regulatory taxa	Barrier dysfunction	Immune overactivation	Systemic inflammation
Osteoarticular diseases	Inflammatory shifts	Indirect impairment	Cytokine signaling	Joint inflammation
Functional syndromes	Altered metabolism	Variable integrity	Bioactive metabolites	Multisystem effects
Chronic inflammation	Persistent dysbiosis	Long-term disruption	Sustained activation	Disease progression

Disease context	Microbiota alteration	Barrier integrity	Inflammatory profile	Systemic outcome
Aging-related conditions	Microbial instability	Reduced resilience	Inflammaging	Functional decline
Multimorbidity	Complex dysbiosis	Combined defects	Amplified cascades	Systemic burden

The reviewed studies revealed consistent associations between gut microbiota composition and host energy metabolism, particularly with respect to enhanced caloric extraction and altered lipid and glucose homeostasis. Specific microbial profiles were linked to increased production of metabolites involved in energy storage, insulin signaling, and adipose tissue regulation. These metabolic alterations were commonly observed in individuals with obesity and metabolic dysfunction, reinforcing the role of microbiota-driven metabolic imbalance.

In addition, several studies reported that shifts in bacterial taxa were associated with impaired metabolic flexibility and low-grade inflammatory responses, suggesting an interaction between metabolic and immune pathways. Altered microbial metabolite profiles were also shown to influence hepatic lipid accumulation and peripheral insulin sensitivity. Together, these findings highlight the contribution of gut microbiota dysbiosis to the pathophysiology of metabolic disease through integrated metabolic and inflammatory mechanisms (Table 2).

Table 2: Gut microbiota and host energy metabolism. This table outlines microbial patterns associated with altered energy harvest and metabolic regulation

Metabolic feature	Microbial pattern	Metabolic pathway	Host effect	Clinical implication
Energy harvest	Enhanced fermentation	SCFA overproduction	Increased caloric uptake	Weight gain
Glucose metabolism	Dysbiosis	Impaired signaling	Insulin resistance	Hyperglycemia
Lipid metabolism	Pro-lipogenic taxa	Altered storage	Adiposity increase	Metabolic syndrome
Bile acid signaling	Modified conversion	Altered receptors	Energy imbalance	Obesity risk
Diet interaction	Microbiota shift	Nutrient utilization	Energy storage	Weight gain
Metabolic flexibility	Reduced diversity	Limited adaptation	Metabolic stress	Disease risk
Inflammatory tone	Chronic dysbiosis	Immune activation	Low-grade inflammation	Chronic disease
Energy balance	Balanced microbiota	Homeostasis	Stable metabolism	Metabolic health
Systemic metabolism	Persistent imbalance	Pathway disruption	Global dysregulation	Multisystem impact

The analyzed studies demonstrated consistent associations between alterations in gut microbiota and disturbances in glucose metabolism characteristic of diabetes mellitus. Dysbiotic microbial profiles were frequently linked to impaired insulin sensitivity, increased inflammatory signaling, and altered intestinal barrier function. These patterns were observed across both type 1 and type 2 diabetes, indicating a shared microbiota-related metabolic imbalance.

Several studies have further reported that diabetes-associated dysbiosis is characterized by reduced microbial diversity and shifts in taxa involved in the production of short-chain fatty acids and immune regulation. These microbial changes were associated with enhanced systemic inflammation and dysregulated glucose homeostasis, suggesting a bidirectional relationship between metabolic control and gut microbiota composition. Collectively, the findings support the role of intestinal dysbiosis as a contributing factor to diabetes pathophysiology through combined metabolic and inflammatory mechanisms (Table 3).

Table 3: Gut microbiota alterations associated with diabetes mellitus. This table summarizes microbiota-related mechanisms linked to glucose dysregulation

Diabetes stage	Microbiota pattern	Barrier status	Inflammatory mechanism	Metabolic outcome
Prediabetes	Intermediate profiles	Mild impairment	Low-grade inflammation	Progression risk
Type 1 diabetes	Reduced diversity	Increased permeability	Immune activation	Glycemic instability
Type 2 diabetes	Dysbiotic taxa	Barrier dysfunction	Insulin resistance	Hyperglycemia
Early diabetes	Microbial shifts	Subclinical leakage	Metabolic stress	Imbalance

Advanced diabetes	Persistent dysbiosis	Chronic disruption	Systemic inflammation	Complications
Insulin resistance	Inflammatory taxa	Altered barrier	Cytokine signaling	Glucose intolerance
Disease progression	Uncontrolled dysbiosis	Barrier failure	Chronic activation	Systemic damage
Metabolic control	Restored balance	Improved integrity	Reduced inflammation	Glycemic improvement
Therapeutic failure	Resistant profiles	Ongoing dysfunction	Persistent signaling	Poor outcomes

The reviewed evidence indicated that specific gut microbial profiles were associated with increased energy harvest from the diet and enhanced fat accumulation. These so-called "fattening bacteria" were consistently linked to altered lipid metabolism, low-grade inflammation, and increased adiposity. Such microbial patterns were predominantly observed in obese individuals, supporting a microbiota-mediated contribution to weight gain and metabolic imbalance.

Additional findings showed that these microbial configurations were often accompanied by reduced microbial diversity and an overrepresentation of taxa involved in energy extraction and lipid storage pathways. Several studies also reported interactions between these bacterial profiles and host genetic or dietary factors, suggesting that microbiota-driven weight gain may result from complex host–microbe–environment interactions. Together, these results reinforce the role of gut microbiota composition as a determinant of obesity-related metabolic dysfunction (Table 4).

Table 4: Gut microbiota and obesity-associated microbial profiles. This table describes patterns linked to fat accumulation and metabolic imbalance

Obesity feature	**Microbial profile**	**Metabolic activity**	**Inflammatory status**	**Systemic effect**
Energy extraction	Fattening bacteria	Enhanced fermentation	Low-grade inflammation	Weight gain
Adiposity	Pro-lipogenic taxa	Fat storage signaling	Chronic activation	Metabolic syndrome
Diet-induced obesity	Microbial shift	Altered nutrient use	Inflammation	Adipose expansion
Visceral fat	Dysbiosis	Lipid dysregulation	Cytokine release	Insulin resistance
Weight maintenance	Balanced microbiota	Energy homeostasis	Controlled inflammation	Stability
Obesity progression	Persistent dysbiosis	Chronic imbalance	Inflammaging	Disease worsening
Metabolic health	Diverse microbiota	Adaptive metabolism	Low inflammation	Reduced risk
Population impact	Widespread dysbiosis	Diet patterns	Chronic inflammation	Public burden
Long-term outcome	Uncorrected imbalance	Sustained activity	Systemic stress	Comorbidities

The synthesized findings demonstrated consistent associations between gut microbiota dysbiosis and the development of musculoskeletal disorders, including inflammatory arthritis and osteoarthritis. Altered microbial profiles were linked to systemic inflammation, joint tissue degradation, and modulation of pain-related pathways. These observations support the presence of a gut–joint axis in which intestinal microbial imbalance contributes to osteoarticular disease processes.

Several studies further indicated that dysbiosis-related inflammatory mediators may influence immune cell activation within joint tissues, thereby exacerbating synovial inflammation and cartilage breakdown. Microbial-derived metabolites were also reported to affect bone remodeling and nociceptive signaling, suggesting a multifactorial impact of the gut microbiota on musculoskeletal health. Collectively, these findings highlight the role of intestinal microbial imbalance as a contributor to both inflammatory and degenerative joint disorders (Table 5).

Table 5: Gut microbiota and osteoarticular diseases. This table summarizes microbiota-related mechanisms in joint pathology

Joint condition	**Microbial alteration**	**Inflammatory pathway**	**Tissue effect**	**Clinical outcome**
Inflammatory arthritis	Dysbiotic taxa	Immune activation	Synovial inflammation	Joint pain
Osteoarthritis	Microbial imbalance	Low-grade inflammation	Cartilage degradation	Reduced mobility
Joint degeneration	Chronic dysbiosis	Cytokine signaling	Tissue breakdown	Functional decline
Pain modulation	Microbial signals	Neuroinflammation	Altered nociception	Chronic pain
Disease progression	Persistent imbalance	Inflammatory cascade	Structural damage	Disability
Early disease	Subtle dysbiosis	Mild inflammation	Reversible changes	Prevention potential
Advanced disease	Severe dysbiosis	Chronic activation	Irreversible damage	Impairment
Aging joints	Microbial instability	Inflammaging	Degeneration	Loss of function
Clinical burden	Long-term dysbiosis	Sustained signaling	Tissue failure	Disability risk

The analyzed literature also identified functional systemic syndromes associated with specific gut microbiota alterations, characterized by the endogenous production of bioactive or toxic metabolites. These microbial activities were linked to measurable systemic effects, including metabolic disturbances and neurophysiological symptoms, independent of external exposures. Such findings indicate that microbial metabolism itself may generate disease phenotypes, reinforcing the concept of functional microbiota-driven syndromes.

Additional evidence suggested that these syndromes were associated with persistent alterations in host–microbe signaling pathways, affecting immune regulation, mitochondrial function, and neural communication. Several studies reported that symptom severity correlated with the abundance of metabolite-producing microbial taxa, supporting a dose-dependent relationship between microbial activity and clinical manifestations. Together, these results underscore the relevance of functional dysbiosis as a mechanistic contributor to systemic disease expression (Table 6).

Table 6: Functional systemic syndromes associated with gut microbiota alterations. This table describes syndromes driven by microbial metabolic activity

Syndrome type	**Microbial activity**	**Metabolite production**	**Physiological effect**	**Clinical manifestation**
Auto-brewery syndrome	Ethanol-producing bacteria	Endogenous ethanol	Neurotoxicity	Intoxication
Metabolic syndromes	Altered fermentation	Bioactive metabolites	Metabolic stress	Systemic symptoms
Neurofunctional disorders	Microbial imbalance	Neuroactive compounds	Neural modulation	Cognitive changes
Fatigue syndromes	Metabolic dysregulation	Inflammatory mediators	Energy imbalance	Chronic fatigue
Functional GI disorders	Microbial shifts	Gas and metabolites	Visceral sensitivity	Abdominal symptoms
Systemic effects	Persistent dysbiosis	Circulating metabolites	Multiorgan impact	Functional impairment
Subclinical syndromes	Low-level imbalance	Mild metabolite output	Hidden effects	Underdiagnosis
Clinical recognition	Microbiota profiling	Mechanistic ID	Targeted therapy	Improved outcomes
Long-term risk	Untreated dysbiosis	Sustained activity	Systemic stress	Chronic disease

The findings summarized in Table 6 highlight the growing body of evidence linking gut microbiota composition to the development and progression of multiple chronic systemic conditions. Across the analyzed studies, microbial dysbiosis was consistently associated with metabolic disturbances, inflammatory pathways, and alterations in host physiological regulation.

The compiled evidence also indicates that variations in microbial diversity and functional metabolic activity may influence disease susceptibility and therapeutic responsiveness in different clinical contexts. Together, these results reinforce the relevance of gut microbiota as a systemic biological factor involved in metabolic regulation, immune modulation, and disease progression. These findings provide the empirical basis for the integrative discussion presented in the following section.

4.0. DISCUSSION

Emerging evidence indicates that gut microbiota dysbiosis may contribute to the pathophysiology of autism spectrum disorder through mechanisms involving altered microbial composition, metabolic imbalance, and immune dysregulation. Children with autism frequently exhibit gastrointestinal symptoms and distinct microbial profiles, suggesting a functional link between intestinal dysbiosis and neurodevelopmental alterations (Sharon *et al.*, 2019; Vuong and Hsiao, 2020; Santana *et al.*, 2024).

Mechanistically, alterations in microbial-derived metabolites, including short-chain fatty acids and neurotransmitter precursors, have been implicated in modulating neural signaling pathways and brain development. Dysregulated immune responses originating in the gut may further influence neuroinflammation and synaptic function through microbiota–immune–brain interactions. In addition, impaired intestinal barrier function has been proposed as a contributor to systemic immune activation, potentially affecting neurodevelopmental trajectories. Together, these findings support the concept of a microbiota-mediated gut–brain axis in autism spectrum disorder, highlighting intestinal dysbiosis as a biologically plausible contributor to neurodevelopmental dysfunction rather than a secondary comorbidity (Figure 7) (Sharon *et al.*, 2019; Vuong and Hsiao, 2020; Santana *et al.*, 2024).

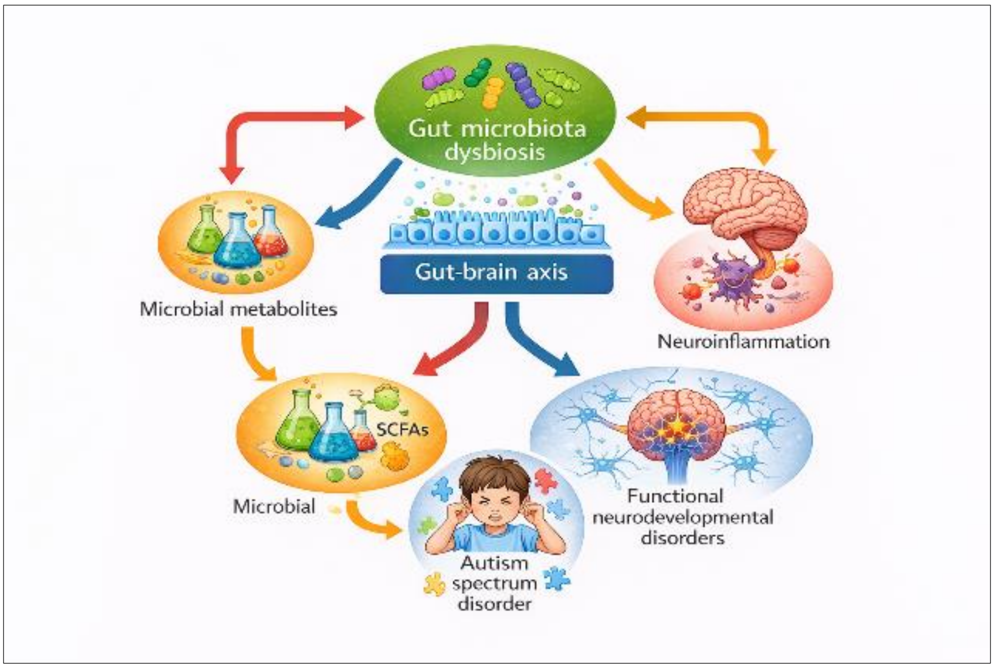

Figure 7: Schematic representation of gut microbiota dysbiosis influencing microbial metabolite production and gut–brain axis signaling. These interactions contribute to neuroinflammatory processes and functional neurodevelopmental alterations. The figure highlights microbiota-mediated mechanisms potentially involved in autism spectrum disorder

Accumulating evidence supports a central role of gut microbiota dysbiosis in the pathophysiology of irritable bowel syndrome, a prototypical disorder of gut–brain interaction. Altered microbial composition, impaired intestinal barrier function, and low-grade immune activation contribute to visceral hypersensitivity and abnormal gut motility. Microbiota-derived metabolites may further modulate neural signaling and pain perception, reinforcing symptom persistence. If these microbiota-mediated mechanisms remain insufficiently targeted, current therapeutic approaches may continue to focus on symptom control rather than disease modification. Future strategies integrating microbiota profiling may enable more effective and personalized management of irritable bowel syndrome (Jeffery *et al.*, 2012; Spiller and Major, 2016; Tap *et al.*, 2017; Lynch and Pedersen, 2024).

These interactions may involve microbial metabolites, neuroinflammatory signaling, and gut–brain communication pathways. If these mechanisms remain insufficiently characterized, future therapeutic strategies may fail to address potentially modifiable biological contributors to autism-related symptoms. Advancing microbiota-targeted research may therefore open new avenues for biomarkers and adjunctive interventions in autism spectrum disorder (Finegold *et al.*, 2010; Cryan and Dinan, 2012; Sharon *et al.*, 2019; Vuong and Hsiao, 2020).

Emerging evidence indicates that gut microbiota interacts directly with cannabinoids, influencing their metabolism, bioavailability, and biological effects. Intestinal microorganisms are capable of transforming phytocannabinoids such as tetrahydrocannabinol and cannabidiol into metabolites with distinct pharmacological activity, thereby modulating anti-inflammatory and neuroprotective responses. In addition, microbiota composition may affect endocannabinoid signaling through indirect regulation of cannabinoid receptors and bile acid metabolism. These interactions suggest that individual variability in microbiota profiles may contribute to heterogeneous clinical responses to cannabinoid-based therapies. Understanding microbiota–cannabinoid interactions may therefore improve therapeutic precision and safety in clinical applications (Cani *et al.*, 2016; Di Marzo and Silvestri, 2019; Cluny *et al.*, 2020; Vijay *et al.*, 2021).

The findings of this integrative review reinforce the concept that gut microbiota dysbiosis represents a central biological mechanism underlying systemic low-grade inflammation across diverse chronic diseases. Rather than acting as isolated disease modifiers, microbial alterations appear to converge on shared inflammatory pathways that influence metabolic, musculoskeletal, and functional outcomes. This convergence supports a systems-based interpretation in which intestinal dysbiosis functions as a unifying pathological driver rather than a condition-specific phenomenon. Pathophysiological cascade linking gut dysbiosis to chronic disease (Figure 8) (Cani *et al.*, 2011; Scher *et al.*, 2013; Belkaid and Harrison, 2017; Fan and Pedersen, 2021; Bufaíçal Filho *et al.*, 2024).

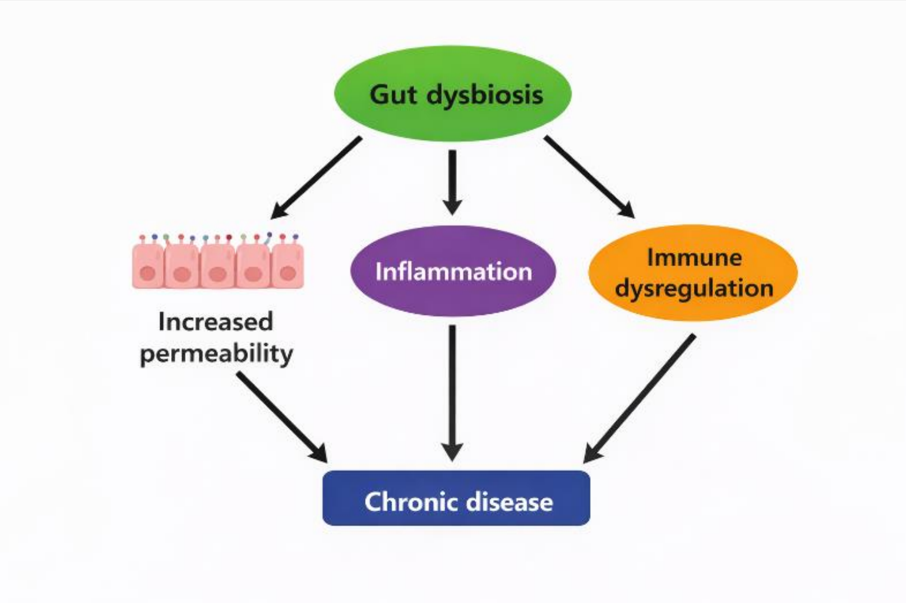

Figure 8: Schematic representation of gut dysbiosis leading to increased intestinal permeability, immune dysregulation, and sustained inflammatory responses. These interconnected processes converge to promote the development and maintenance of chronic diseases. The figure emphasizes dysbiosis as a central trigger of systemic pathological cascades

A major current challenge in microbiota research lies in the fragmentation of evidence across isolated disease models, which limits the translation of microbiome findings into clinical practice. Most studies continue to address metabolic, musculoskeletal, or autoimmune disorders independently, despite shared inflammatory and microbial mechanisms. If this reductionist approach persists, future research risks generating incremental knowledge without producing integrative diagnostic or therapeutic advances. Addressing this gap requires a systemic framework capable of unifying microbiota-driven mechanisms across diseases. Fragmentation of microbiota research across disease-specific models (Figure 9) (Turnbaugh *et al.*, 2007; Qin *et al.*, 2010; Lynch and Pedersen, 2016; Fan and Pedersen, 2021; Santana *et al.*, 2025).

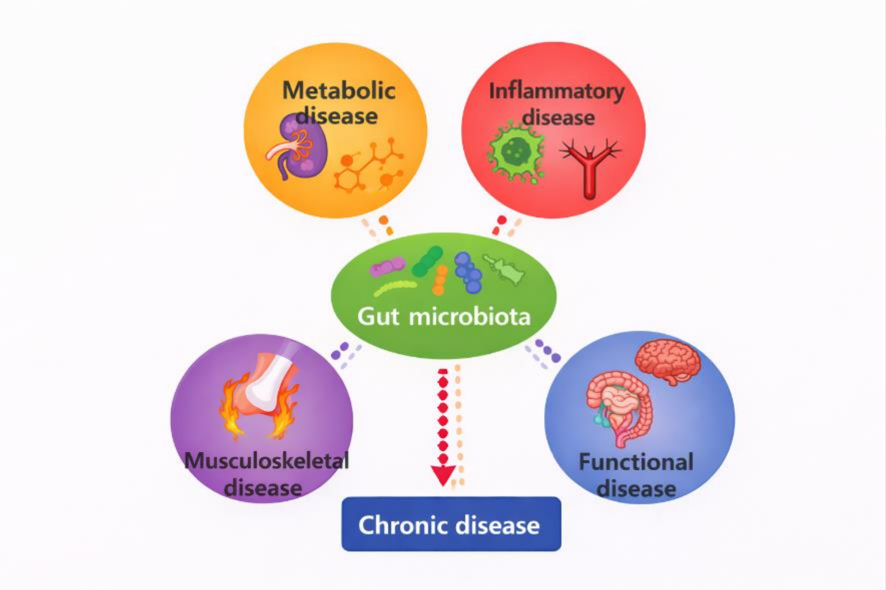

Figure 9: Schematic representation of isolated research approaches addressing metabolic, inflammatory, musculoskeletal, and functional diseases independently. The figure illustrates the lack of integration among disease models despite shared microbiota-driven mechanisms. This fragmentation limits the translation of microbiota research into systemic clinical applications

Another major current limitation involves the difficulty in establishing causal relationships between specific microbial profiles and systemic disease outcomes. Much of the existing evidence relies on cross-sectional designs, heterogeneous methodologies, and inconsistent microbiota profiling techniques, which restrict comparability and clinical applicability. If these limitations persist, future microbiota-based interventions may lack reproducibility and regulatory acceptance. Advancing the field will require standardized protocols, longitudinal studies, and mechanistic validation to support causal inference. Integrated microbiota-based framework for personalized disease management (Figure 10) (Zhao *et al.*, 2018; Falony *et al.*, 2019; Vujkovic-Cvijin *et al.*, 2020; Lynch and Pedersen, 2024).

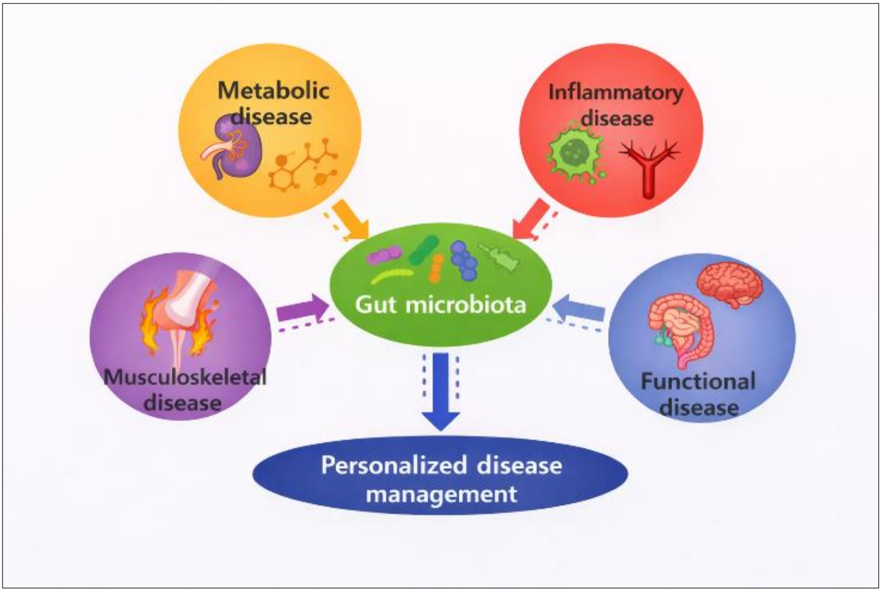

Figure 10: Schematic representation of the gut microbiota as a central modulator connecting metabolic, inflammatory, musculoskeletal, and functional disease domains. These interconnected pathways converge toward individualized therapeutic strategies. The figure highlights the role of microbiota-driven integration in precision medicine

Despite growing scientific interest, the clinical translation of microbiota-based interventions remains limited by variability in patient responses and a lack of standardized therapeutic protocols. Current approaches, such as probiotics, dietary modulation, and fecal microbiota transplantation, show inconsistent efficacy across various disease contexts, reflecting an incomplete understanding of host–microbe interactions. If these challenges are not addressed, future clinical applications risk remaining empirical rather than precision-based. Progress will depend on personalized strategies integrating microbial, metabolic, and immunological profiling. Microbiota-driven pathways shaping precision medicine strategies (Figure 11) (Smits *et al.*, 2013; Cammarota *et al.*, 2017; Vrieze *et al.*, 2020; Lynch and Pedersen, 2024).

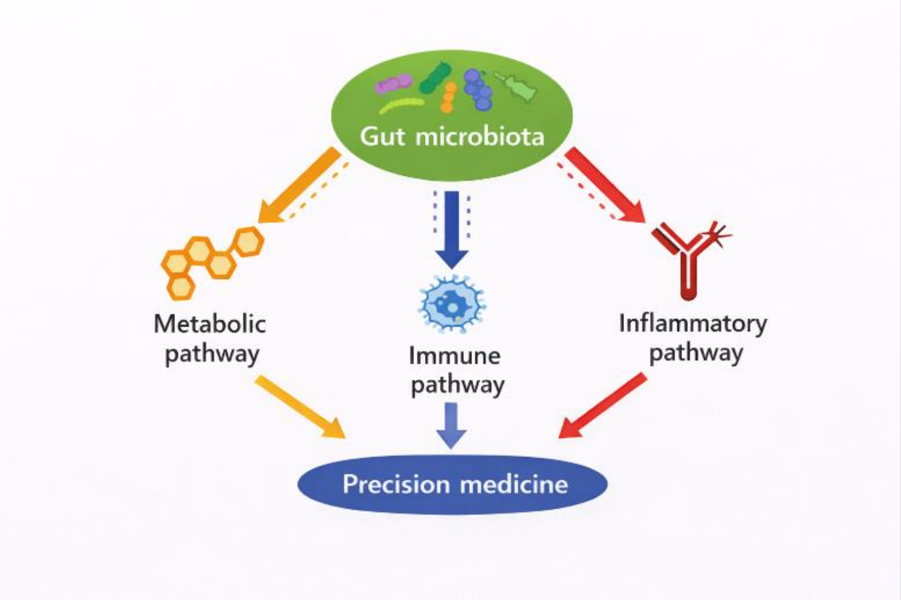

Figure 11: Schematic representation of gut microbiota–host interactions integrating metabolic, immune, and inflammatory pathways. These interconnected mechanisms support individualized risk stratification and therapeutic targeting. The figure highlights the role of microbiota-based frameworks in advancing precision medicine

Recent randomized clinical evidence further supports the concept that interindividual variability in therapeutic response may be microbiota-dependent rather than purely behavioral or genetic. In a large, open-label, randomized trial involving 802 individuals with prediabetes, dietary fiber supplementation did not result in significant glycemic improvement at the population level. However, post-hoc clustering revealed that participants belonging to metabolically distinct microbiota-associated phenotypes exhibited significant reductions in HbA1c following intervention, while others showed no benefit. Machine-learning-based microbiome clinical decision models were able to predict glycemic response to fiber intake, suggesting that baseline microbial composition may determine intervention efficacy. These findings reinforce the need for microbiota-guided nutritional strategies and highlight the limitations of uniform dietary recommendations in metabolic disease prevention (Song *et al.,* 2025).

The association between gut microbiota composition and obesity highlights a major current public health concern, particularly regarding microbial profiles that enhance energy harvest and fat accumulation. These so-called fattening bacteria contribute to metabolic imbalance through altered lipid metabolism and chronic low-grade inflammation, reinforcing obesity as a microbiota-modulated condition rather than solely a behavioral disorder. If unaddressed, this paradigm shift implies a future increase in obesity-related comorbidities resistant to conventional lifestyle interventions. Integrating microbiota-targeted strategies into public health frameworks may therefore be essential for effective prevention and long-term metabolic control. Obesity-related gut microbiota and systemic metabolic imbalance (Figure 12) (Ley *et al.*, 2006; Turnbaugh *et al.*, 2006; Ridaura *et al.*, 2013; Pedersen, 2021; Lynch and Pedersen, 2024; Santana *et al.*, 2025a).

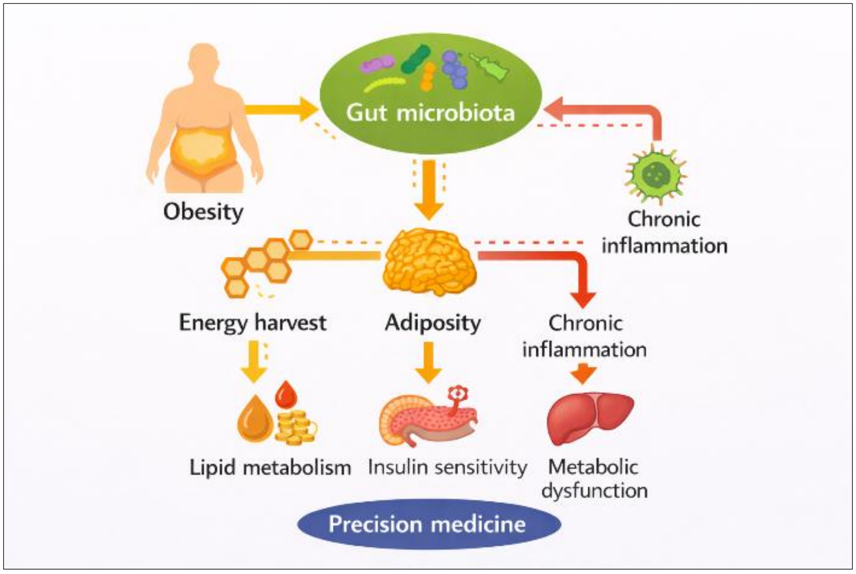

Figure 12: Schematic representation of gut microbiota profiles associated with increased energy harvest, adiposity, and chronic low-grade inflammation. Microbial alterations influence lipid metabolism, insulin sensitivity, and inflammatory signaling pathways. The figure highlights the contribution of dysbiosis to obesity-related systemic dysfunction

The relationship between gut microbiota dysbiosis and diabetes mellitus represents a critical current challenge, as microbial alterations are increasingly linked to impaired glucose regulation, insulin resistance, and systemic inflammation. These interactions suggest that diabetes progression may be driven not only by host genetics and lifestyle factors but also by persistent microbiota-mediated metabolic dysfunction. If this mechanism remains insufficiently addressed, future therapeutic strategies may fail to halt disease progression and associated complications. Targeting microbial pathways may therefore become a necessary component of effective diabetes management and prevention strategies. Gut microbiota dysbiosis as a driver of diabetes mellitus progression (Figure 13) (Qin *et al.*, 2012; Karlsson *et al.*, 2013; Gurung *et al.*, 2020; Lynch and Pedersen, 2024).

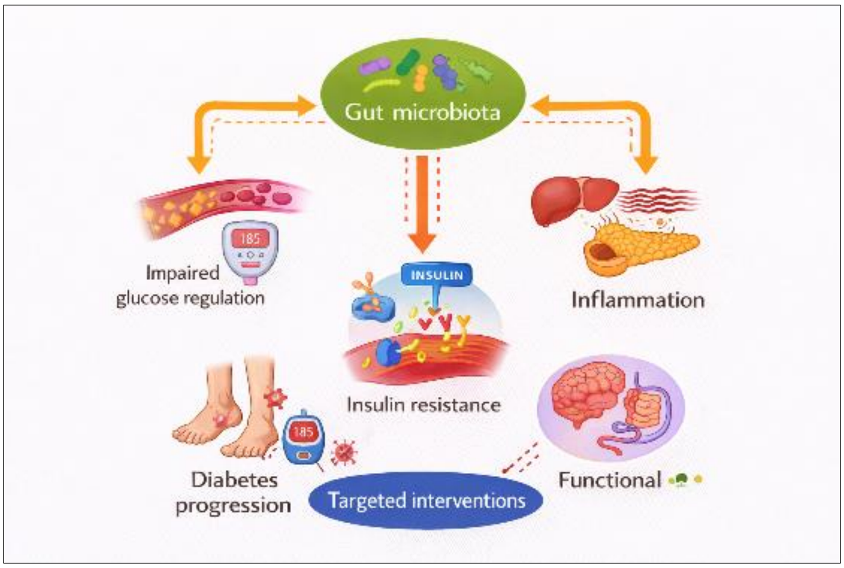

Figure 13: Schematic representation of microbial alterations associated with impaired glucose regulation, insulin resistance, and systemic inflammation. These microbiota-driven interactions contribute to diabetes progression beyond genetic and lifestyle factors. The figure highlights microbial pathways as potential targets for diabetes prevention and management strategies

Recent randomized clinical evidence further supports the concept that interindividual variability in therapeutic response may be microbiota-dependent rather than purely behavioral or genetic. In a large, open-label, randomized trial involving 802 individuals with prediabetes, dietary fiber supplementation did not result in significant glycemic improvement at the population level. However, post-hoc clustering revealed that participants belonging to metabolically distinct microbiota-associated phenotypes exhibited significant reductions in HbA1c following intervention, while others showed no benefit. Machine-learning-based microbiome clinical decision models were able to predict glycemic response to fiber intake, suggesting that baseline microbial composition may determine intervention efficacy. These findings reinforce the need for microbiota-guided nutritional strategies and highlight the limitations of uniform dietary recommendations in metabolic disease prevention (Song *et al.,* 2025; Perkins, 2026).

In addition to dietary modulation, growing evidence indicates that gut microbiota composition may influence the pharmacokinetics, efficacy, and toxicity of antidiabetic drugs, a field now described as Pharmacomicribiomics. Microbial metabolism has been shown to modulate the therapeutic effects of commonly used agents such as metformin and sodium–glucose cotransporter-2 inhibitors, potentially affecting glycemic control and cardiovascular outcomes. These drug–microbiota interactions may partially explain interindividual variability in treatment response and adverse effects. Integrating microbiome profiling into pharmacological decision-making may therefore represent a promising strategy to optimize therapeutic efficacy and minimize drug-related complications in type 2 diabetes management (Wen, 2026).

Supporting this concept, recent prospective evidence demonstrated that baseline gut microbiome composition may predict therapeutic response to modern glucose-lowering agents, including semaglutide and empagliflozin. In patients with type 2 diabetes, distinct microbial signatures present before treatment initiation were associated with subsequent improvements in glycohaemoglobin levels over a 12-month follow-up period. Although overall microbial diversity remained unchanged, specific taxa shifts were correlated with treatment efficacy, particularly among individuals initiating GLP-1 receptor agonist therapy. These findings position the gut microbiome as a potential predictive biomarker capable of guiding individualized pharmacological strategies in diabetes management (Figure 14) (Klemets *et al.,* 2026).

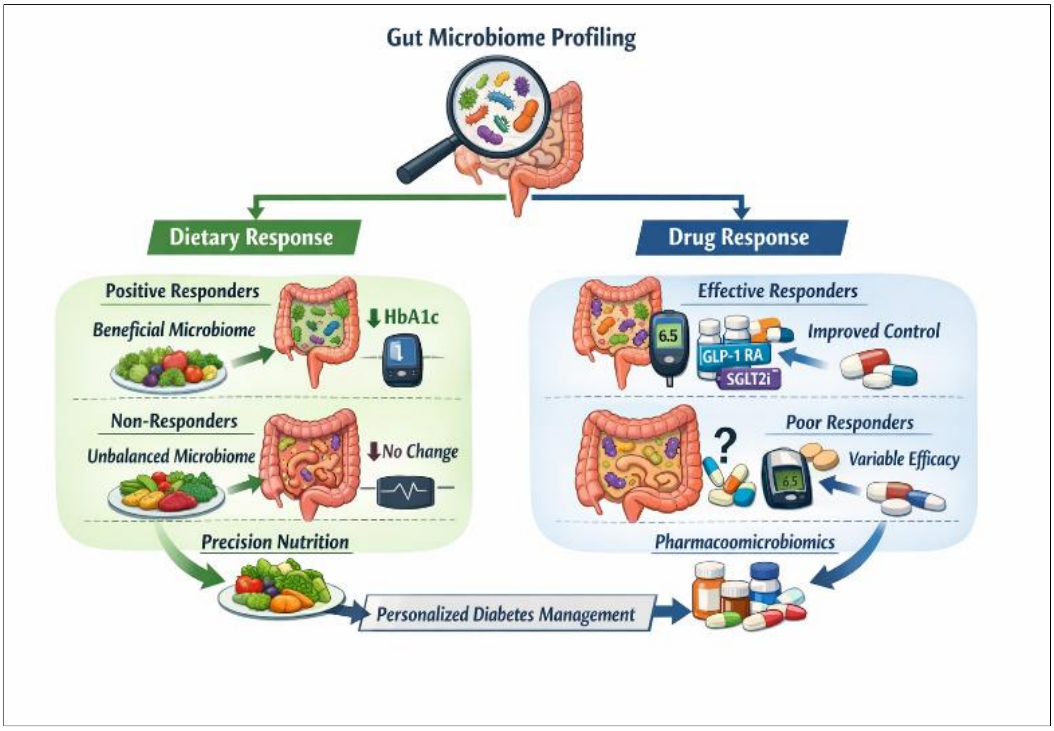

Figure 14: Gut microbiota composition influences interindividual variability in dietary and pharmacological responses in metabolic disease. Distinct microbial profiles determine glycemic response to fiber intake and modulate the efficacy and toxicity of antidiabetic drugs. Microbiome-based stratification may enable precision nutrition and pharmacomicribiomics approaches for personalized diabetes management

The association between gut microbiota dysbiosis and osteoarticular diseases represents a growing current concern, particularly in the context of chronic pain, joint degeneration, and reduced functional capacity. Microbiota-mediated inflammation has been implicated in cartilage degradation and immune activation within joint tissues, contributing to both inflammatory arthritis and osteoarthritis. If these mechanisms remain insufficiently targeted, future aging populations may face increased disability and healthcare burden associated with musculoskeletal decline. Understanding the gut–joint axis may therefore be essential for developing preventive strategies aimed at preserving mobility and quality of life. Microbiota-based therapeutic strategies targeting systemic diseases (Figures 15-16) (Scher *et al.*, 2013; Boer *et al.*, 2019; Favazzo *et al.*, 2020; Huang *et al.*, 2022).

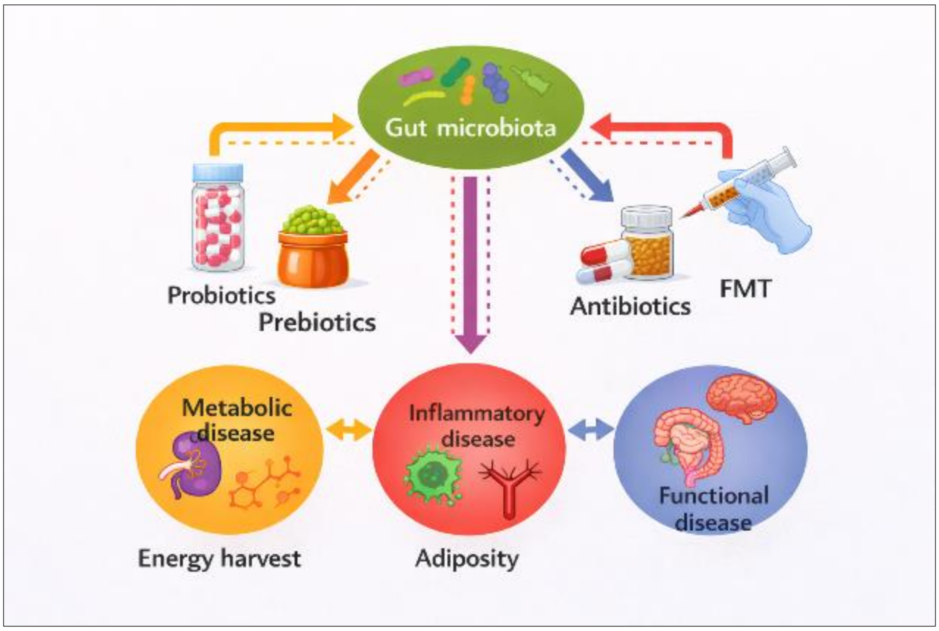

Figure 15: Schematic representation of therapeutic approaches aimed at modulating gut microbiota, including probiotics, prebiotics, antibiotics, and fecal microbiota transplantation. These interventions influence metabolic, inflammatory, and functional disease pathways. The figure highlights microbiota modulation as a central strategy for systemic disease management

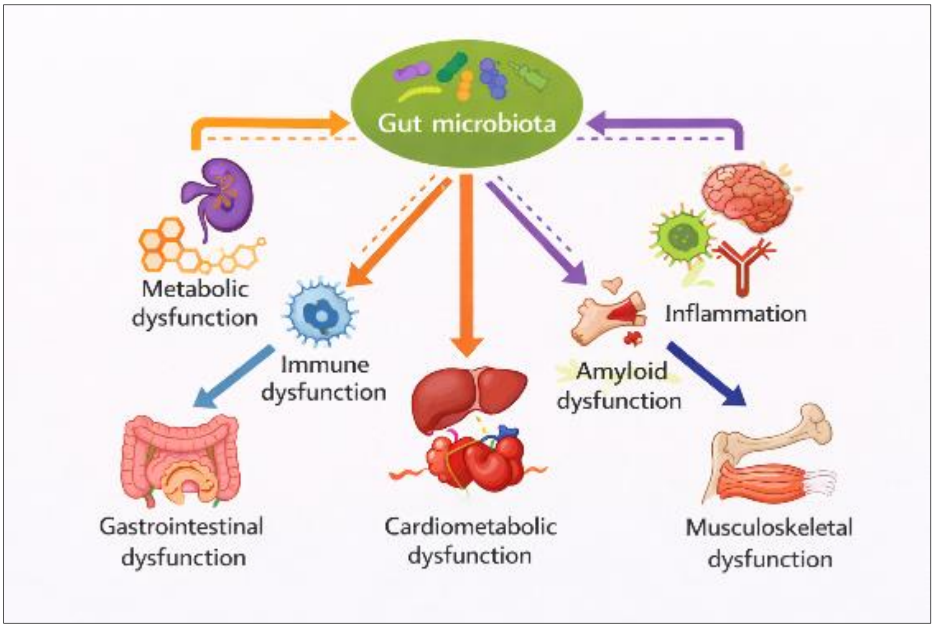

Figure 16: Schematic representation of gut microbiota alterations influencing metabolic, immune, inflammatory, and functional pathways. These interconnected effects impact diverse organs and physiological systems simultaneously. The figure highlights dysbiosis as a central driver of multisystem disease interactions

Recent evidence indicates that gut microbiota composition may influence cognitive aging through modulation of the gut–brain axis, even in the absence of overt disease. Distinct microbial profiles in healthy older adults have been associated with differences in spontaneous cortical activity within brain regions involved in memory, language, and emotional processing. These interactions may be mediated by vagal signaling, inflammatory pathways, and microbiota-derived metabolites that influence neuronal function

(Cryan *et al.*, 2019; Santana *et al.*, 2025a; Santana *et al.*, 2025b; Santana *et al.*, 2025c; Serrano *et al.*, 2025).

Importantly, such findings suggest that cognitive decline is not solely determined by neurodegenerative processes but may also reflect microbiota-related functional variability. If these mechanisms remain underexplored, opportunities for early preventive strategies targeting age-related cognitive deterioration may be missed. Nutritional modulation of gut microbiota, therefore, emerges as a promising approach to preserve cognitive function during aging (Cryan and Dinan, 2012; Sharon *et al.*, 2016).

Increasing evidence supports the concept that gut microbiota modulation represents a promising prophylactic strategy for preventing chronic systemic diseases. Maintenance of microbial eubiosis contributes to intestinal barrier integrity, immune homeostasis, and metabolic balance, thereby reducing the risk of persistent low-grade inflammation. Early-life microbiota disturbances and long-term dysbiosis may predispose individuals to metabolic, inflammatory, and functional disorders later in life. If preventive strategies targeting microbiota composition and function are not adequately implemented, opportunities for disease prevention may be missed. Future prophylactic approaches integrating microbiota profiling may enable personalized interventions aimed at reducing disease susceptibility before clinical onset (Valdes *et al.*, 2018; Zmora *et al.*, 2019; Fan and Pedersen, 2021; Lynch and Pedersen, 2024).

The relationship between gut microbiota and carcinogenesis involves complex interactions between microbial composition, inflammation, and host cellular integrity. Dysbiosis has been associated with the production of pro-inflammatory and genotoxic metabolites that promote tumor initiation and progression, while beneficial bacteria contribute to intestinal barrier function and immune regulation. Cannabidiol has demonstrated antimicrobial activity against resistant bacterial species and anti-inflammatory effects that may indirectly influence microbiota-mediated cancer pathways. Furthermore, gut–brain and gut–immune axis dysregulation driven by chronic stress may exacerbate microbiota alterations associated with cancer risk. Integrating microbiota modulation with cannabinoid-based strategies may represent a novel adjunctive approach in cancer prevention and supportive care (Figure 17) (Schwabe and Jobin, 2013; Zitvogel *et al.*, 2018; Fiorentino *et al.*, 2020; Vivarelli *et al.*, 2021; Bufaíçal Filho *et al.,* 2024).

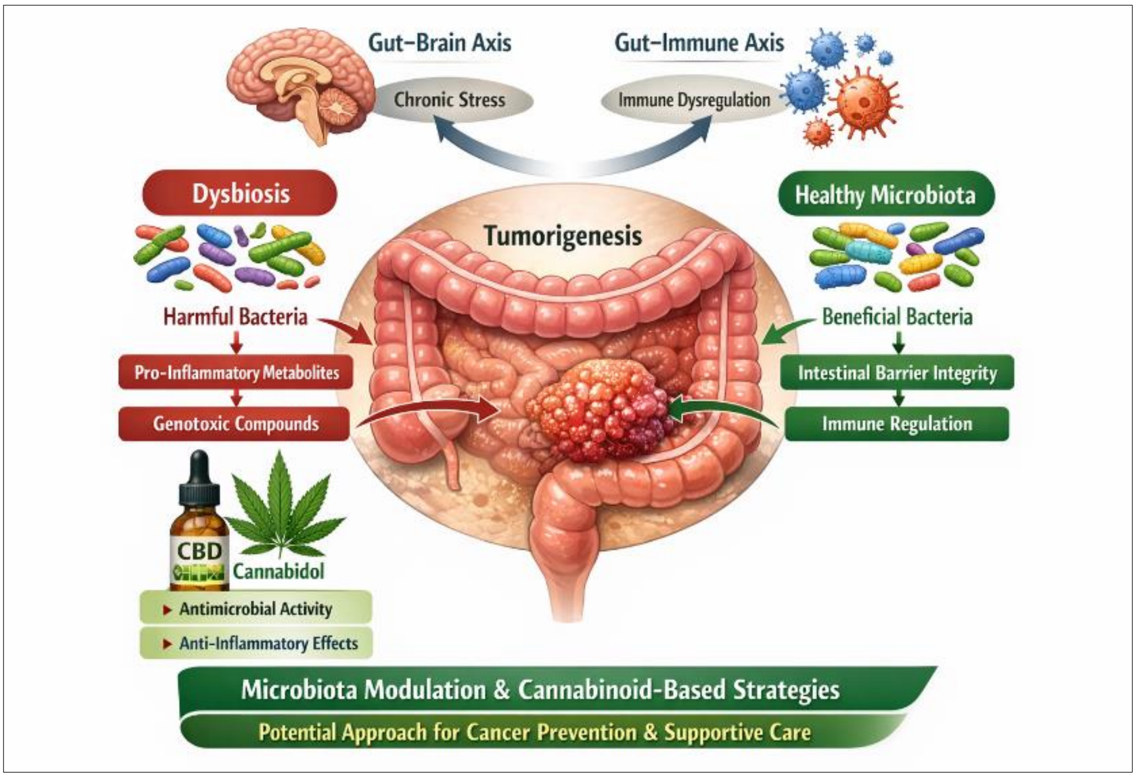

Figure 17: interactions between gut microbiota and carcinogenesis, highlighting the role of dysbiosis, inflammation, and genotoxic metabolites in tumor progression. Beneficial bacteria contribute to intestinal barrier integrity and immune regulation, modulating cancer risk. Cannabidiol may indirectly influence these processes through antimicrobial and anti-inflammatory effects, impacting the gut–brain and gut–immune axes

Emerging evidence suggests that the human microbiota can influence the severity of food allergies through the microbial metabolism of allergenic proteins. In peanut allergy, an IgE-mediated condition triggered mainly by the allergens Ara h1 and Ara h2, certain bacteria present in the oral cavity and small intestine can degrade these proteins, reducing their ability to bind IgE and activate mast cells. Species of the genus *Rothia* Georg and Brown 1967 (Bacteria: Micrococcales: Micrococcaceae) have demonstrated this capacity, producing modified protein fragments with lower allergenic potential. Experimental studies indicate that colonization with *Rothia* decreases allergen levels and attenuates anaphylactic responses. Consistently, individuals with milder peanut allergies tend to harbor higher abundances of allergen-degrading bacteria, suggesting that microbial metabolism of food allergens represents a microbiota-mediated pathway capable of modulating IgE-dependent allergic reactions and may support future microbiome-based therapeutic strategies (Figure 18) (Sánchez-Martínez, 2026).

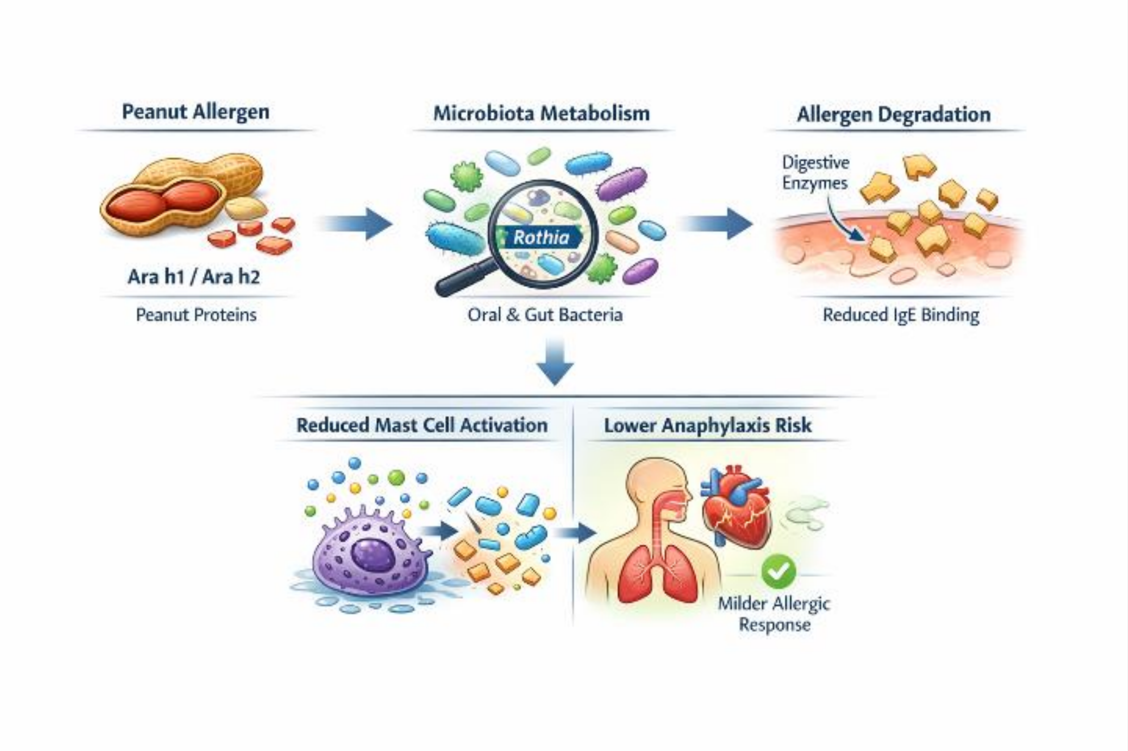

Figure 18: Microbiota-mediated modulation of peanut allergy severity. Oral and intestinal microbiota, particularly *Rothia* species Georg and Brown 1967 (Bacteria: Micrococcales: Micrococcaceae), can metabolize peanut allergens such as Ara h1 and Ara h2, reducing their ability to bind IgE antibodies. This process limits mast cell activation and attenuates allergic responses, suggesting a potential role for microbiome-based strategies in reducing the severity of food-induced anaphylaxis

Looking forward, the integration of gut microbiota research into precision medicine represents a critical opportunity to transform the management of chronic systemic diseases. Advances in multi-omics technologies, biomarker discovery, and individualized microbial profiling may enable targeted interventions that modify disease trajectories rather than merely alleviate symptoms. If successfully implemented, such strategies could redefine preventive and therapeutic paradigms across metabolic, musculoskeletal, and functional disorders. The future of microbiota-based medicine, therefore, depends on interdisciplinary collaboration, regulatory alignment, and sustained investment in translational research frameworks. Gut microbiota–based precision medicine framework for future clinical application (Figure 19) (Zhang *et al.*, 2019; Valdes *et al.*, 2021; Quigley, 2022; Lynch and Pedersen, 2024).

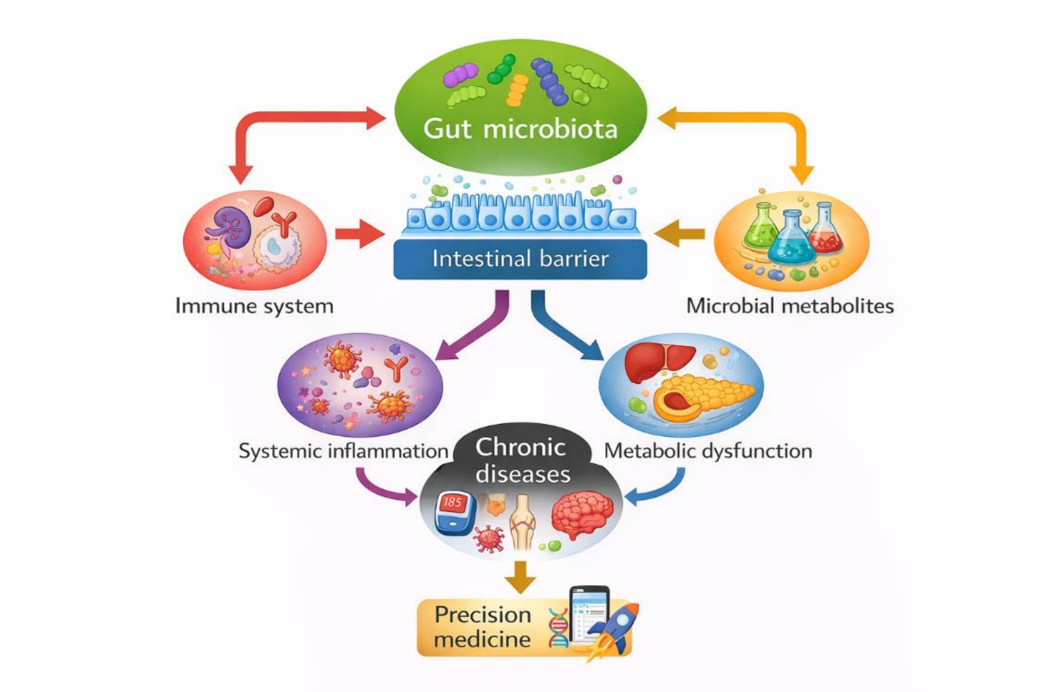

Figure 19: Graphical summary. Gut microbiota–centered framework linking chronic diseases to precision medicine. Schematic overview illustrating gut microbiota as a central regulator connecting intestinal barrier function, immune responses, microbial metabolites, and systemic inflammation. These interconnected mechanisms drive metabolic dysfunction and chronic disease development. The framework highlights the transition from microbiota-driven pathology to precision medicine strategies

5.0. CONCLUSION

The accumulated evidence reviewed in this study supports the concept that gut microbiota functions not only as a contributor to systemic inflammation and metabolic dysfunction but also as a determinant of individual therapeutic response across diverse chronic diseases. Emerging clinical data indicate that microbiota composition may influence the efficacy of dietary interventions and pharmacological treatments, including glucose-lowering agents commonly used in type 2 diabetes management. Interindividual variability in microbiome profiles may therefore underline heterogeneous treatment outcomes observed in clinical practice.

Integrating microbiota-based biomarkers into diagnostic and therapeutic decision-making frameworks may enable the identification of patient subgroups most likely to benefit from specific nutritional or pharmacological interventions. Such an approach has the potential to shift current treatment paradigms from standardized protocols toward individualized microbiome-guided strategies aimed at improving therapeutic efficacy and minimizing adverse effects. Future translational research combining longitudinal clinical studies with multi-omics profiling and predictive modeling will be essential to validate microbiota-informed precision medicine as a viable strategy for the prevention and management of chronic systemic diseases.

REFERENCES

- Belkaid, Y., & Harrison, O. J. (2017). Homeostatic immunity and the microbiota. *Immunity*, *46*(4), 562–576.
- Belkaid, Y., & Harrison, O. J. (2021). The microbiota in immunity and inflammation. *Nature Reviews Immunology*, *21*(1), 9–23.
- Boer, C. G. *et al.* (2019). Intestinal microbiome composition and its relation to joint pain and inflammation. *Nature Communications*, *10*(1), 4881.
- Bufaíçal Filho, R. F., Marchiori, C. H., & Malheiros, K. P. (2024). Relationship of the endocannabinoid system with hormonal functions. *Journal of Medical Sciences of the Middle East*, *4*(6), 245–260.
- Cammarota, G. *et al.* (2017). European consensus conference on faecal microbiota transplantation. *Gut*, *66*(4), 569–580.
- Cani, P. D. *et al.* (2011). Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*, *56*(7), 1761–1772.
- Cani, P. D., Osto, M., Geurts, L., & Everard, A. (2012). Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes. *Current Opinion in Lipidology*, *23*(1), 1–8.
- Cryan, J. F. *et al.* (2019). The microbiota–gut–brain axis. *Physiological Reviews*, *99*(4), 1877–2013.
- Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: The impact of the gut microbiota

on brain and behaviour. *Nature Reviews Neuroscience*, *13*(10), 701–712.

- Engevik, M. A. *et al.* (2020). Human-derived bifidobacterium promotes intestinal barrier function. *Gut Microbes*, *11*(2), 354–365.
- Falony, G. *et al.* (2019). Population-level analysis of gut microbiome variation. *Science*, *352*(6285), 560–564.
- Fan, Y., & Pedersen, O. (2021). Gut microbiota in human metabolic health and disease. *Nature Reviews Microbiology*, *19*(1), 55–71.
- Favazzo, L. J. *et al.* (2020). The gut microbiome–joint connection. *Journal of Bone and Mineral Research*, *35*(6), 1091–1100.
- Gurung, M. *et al.* (2020). Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine*, *51*, 102590.
- Huang, Z., Kraus, V. B., & Ren, Z. (2022). Gut microbiome and osteoarthritis. *Arthritis & Rheumatology*, *74*(6), 924–933.
- Karlsson, F. H. *et al.* (2013). Gut metagenome in European women with normal, impaired, and diabetic glucose control. *Nature*, *498*(7452), 99–103.
- Klemets, A. *et al*. (2026). Fecal microbiome predicts treatment response after the initiation of semaglutide or empagliflozin uptake. *Scientific Reports, 16*(1), 6126.
- Koh, A., De Vadder, F., Kovatcheva-Datchary, P., & Bäckhed, F. (2016). From dietary fiber to host physiology. *Cell*, *165*(6), 1332–1345.
- Ley, R. E., Turnbaugh, P. J., Klein, S., & Gordon, J. I. (2006). Microbial ecology: Human gut microbes associated with obesity. *Nature*, *444*(7122), 1022–1023.
- Logan, A. C., Jacka, F. N., & Prescott, S. L. (2019). Immune–microbiota interactions. *Nutrients*, *11*(10), 2470.
- Lynch, S. V., & Pedersen, O. (2016). The human intestinal microbiome in health and disease. *New England Journal of Medicine*, *375*(24), 2369–2379.
- Lynch, S. V., & Pedersen, O. (2024). The microbiome in precision medicine. *Science*, *383*(6683), eabn7980.
- Nekoukar, Z., Zamani, M., Ghasemi, A., & Nejadghaderi, S. A. (2021). Microbiota and chronic inflammation. *Clinical Nutrition*, *40*(4), 1905–1914.
- Perkins, A. (2026). Gut microbiome predicts response to diabetes drugs. Retrieved, Feb, 24, 2026, fromhttps://www.emjreviews.com/diabetes/news/gut-microbiome-predicts-response-to-diabetes-drugs/
- Qin, J. *et al.* (2010). A human gut microbial gene catalogue. *Nature*, *464*(7285), 59–65.
- Qin, J. *et al.* (2012). A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature*, *490*(7418), 55–60.
- Quigley, E. M. M. (2021). Gut microbiota and the role in functional gastrointestinal disorders. *Gastroenterology*, *160*(1), 47–60.
- Quigley, E. M. M. (2022). Microbiota–brain interactions. *Gastroenterology*, *162*(3), 698–709.
- Ridaura, V. K. *et al.* (2013). Gut microbiota from twins discordant for obesity. *Science*, *341*(6150), 1241214.
- Sánchez-Martínez, E. *et al.* (2026). Microbial metabolism of food allergens determines the severity of IgE-mediated anaphylaxis. *Cell Host & Microbe, 34*(3), 359-544.
- Santana, M. V. O., Malheiros, K. P., Marchiori, C. H., & Melo, E. M. (2025c). Study the immune system, emphasizing immunological memory, neuroimmunology, immunological placebo effect, and therapeutic updates of the immune system. *Scholars International Journal of Traditional and Complementary Medicine*, *8*(7), 158–187.
- Santana, M. V. O., Marchiori, C. H., & Malheiros, K. P. (2024). The use of repetitive transcranial magnetic stimulation on the microbiota–gut–brain axis, depression, irritable bowel syndrome, and autism. *Middle East Research Journal of Medical Sciences*, *4*(6), 159–173.
- Santana, M. V. O., Marchiori, C. H., Malheiros, K. P., & Melo, E. M. (2025a). Fatty bacteria in the intestine and collagen bacteria (Dominio: Bacteria Woese, Kandler & Wheelis 1990): Therapies and biotechnology. *Middle East Research Journal of Medical Sciences*, *5*(1), 29–48.
- Santana, M. V. O., Marchiori, C. H., Malheiros, K. P., & Melo, E. M. (2025b). Bacteria cause diabetes mellitus: An integrative review. *MedCrave Online Journal of Biology and Medicine*, *10*(2), 101–112.
- Scher, J. U. *et al.* (2013). Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis. *eLife*, *2*, e01202.
- Serrano, J. I. *et al.* (2025). Gut microbiota profiles are associated with different spontaneous cortical activity in healthy older people. *Scientific Reports*, *15*, 16090.
- Sharon, G., Sampson, T. R., Geschwind, D. H., & Mazmanian, S. K. (2016). The central nervous system and the gut microbiome. *Cell*, *167*(4), 915–932.
- Smits, L. P., Bouter, K. E., de Vos, W. M., Borody, T. J., & Nieuwdorp, M. (2013). Therapeutic potential of fecal microbiota transplantation. *Gastroenterology*, *145*(5), 946–953.
- Tremaroli, V., & Bäckhed, F. (2012). Functional interactions between the gut microbiota and host metabolism. *Nature*, *489*(7415), 242–249.
- Turnbaugh, P. J. *et al.* (2006). An obesity-associated gut microbiome. *Nature*, *444*(7122), 1027–1031.
- Turnbaugh, P. J. *et al.* (2009). A core gut microbiome in obese and lean twins. *Nature*, *457*(7228), 480–484.

- Valdes, A. M., Walter, J., Segal, E., & Spector, T. D. (2021). Role of the gut microbiota in nutrition and health. *BMJ*, *361*, k2179.
- Vrieze, A. *et al.* (2020). Transfer of intestinal microbiota and insulin sensitivity. *Gastroenterology*, *143*(4), 913–916.
- Vujkovic-Cvijin, I., Sklar, J., Jiang, L., Natarajan, L., Knight, R., & Belkaid, Y. (2020). Host variables shape the gut microbiota. *Nature*, *587*(7834), 448–454.
- Wen, D. (2026). Pharmacomicrobiomics: Exploring the role of gut microbiota in type 2 diabetes and antidiabetic drug mechanisms. *Nutrition, Metabolism and Cardiovascular Diseases, 36*(2), 104379.
- Zhang, Y., Zhang, H., Chen, T., & Li, Z. (2019). Gut microbiota in human metabolic diseases. *Journal of Diabetes Research*, *2019*, 1–12.
- Zhao, L. *et al.* (2018). Gut bacteria are selectively promoted by dietary fibers. *Science*, *359*(6380), 1151–1156.
- Zhao, Y., Wu, J., Li, J., Zhou, N., Tang, H., & Wang, Y. (2023). Gut microbiota and host metabolic regulation. *Frontiers in Endocrinology*, *14*, 1184556.